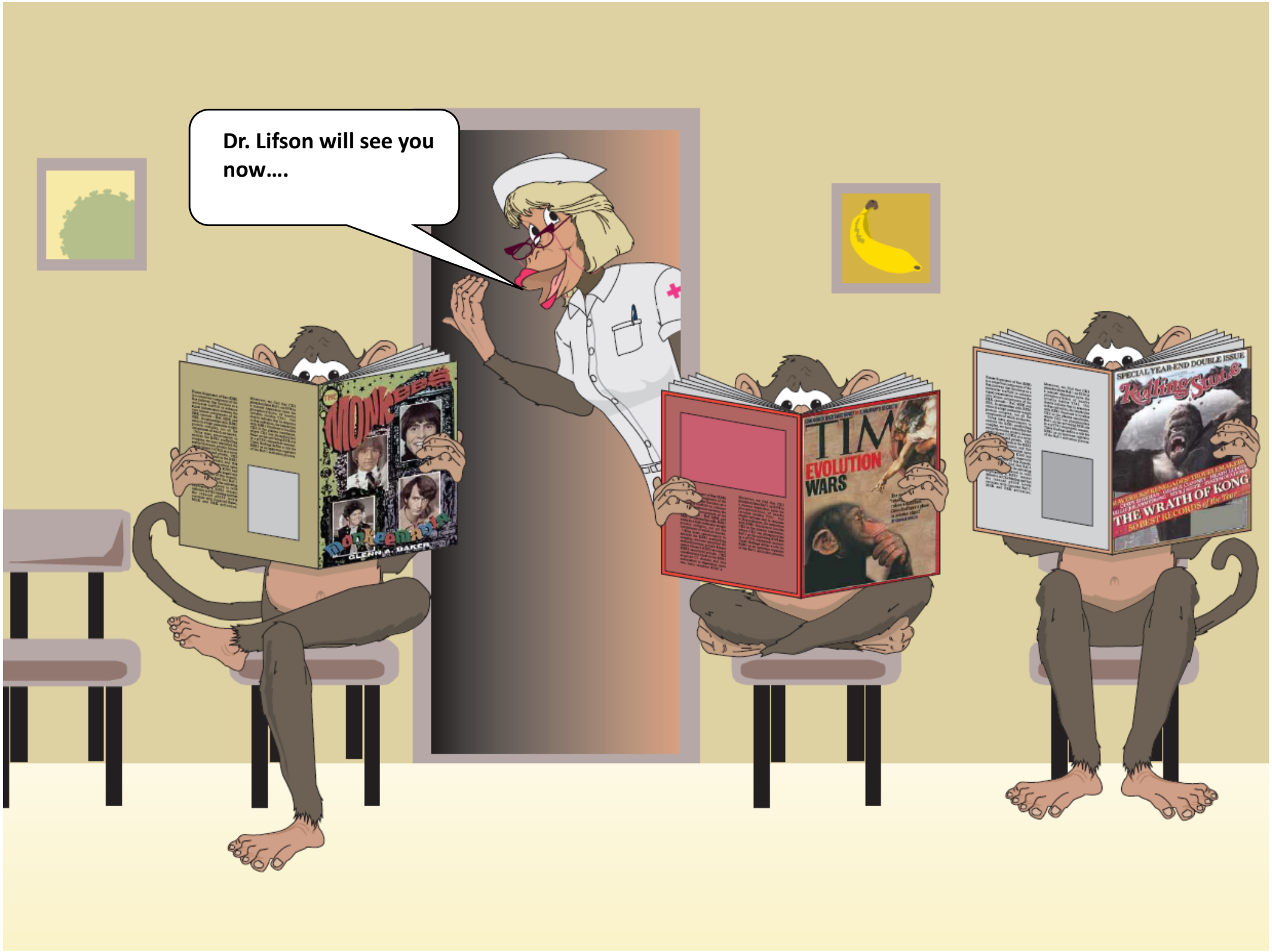
Demystifying Medicine Confession

"Patient"


Dr. Lifson will see you now....
THE MONKEES
monkeemania
GLENN A. BAKER
TIME
EVOLUTION WARS
SPECIAL YEAR-END DOUBLE ISSUE
Rolling Stone
THE WRATH OF KONG
50 BEST RECORDS of the Year

Demystifying Medicine Confession

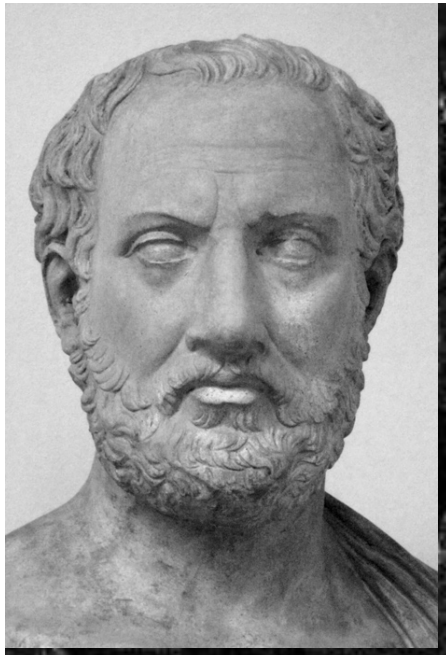
"Patient"

Disclaimer

HIV Vaccine Development

FOR

Sophisticated, Intelligent Non-specialists



Acquired Immunity:

Thucydides on the Plague of Athens in History of the Peloponnesian War, 431 BC

Yet it was with those who had recovered from the disease that the sick and the dying found most compassion. These knew what it was from experience, and had now no fear for themselves; for **the same man was never attacked twice**- never at least fatally. And such persons not only received the congratulations of others, but themselves also, in the elation of the moment, half entertained the vain hope that they were for the future safe from any disease whatsoever.

https://www.google.com/search?q=thucydides,+athenian+plague&source=lnms&tbm=isch&sa=X&ved=0ahUKEwim9qaymJfSAhVBSCYKHfHA1kQ_AUICCgB&biw=1616&bih=824#tbm=isch&q=thucydides%2C+&imgrc=iUsPDh-C06hLbM:

Vaccines Licensed for Use in the United States

https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

Anthrax Vaccine Adsorbed

BCG Live

BCG Live

Cholera Vaccine Live Oral

Diphtheria & Tetanus Toxoids Adsorbed

Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed

Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed

Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine

Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) & Hepatitis B Vaccine (Recombinant)

Hepatitis A Vaccine, Inactivated

Hepatitis A Vaccine, Inactivated

Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine

Hepatitis B Vaccine (Recombinant)

Hepatitis B Vaccine (Recombinant)

Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant

Human Papillomavirus 9-valent Vaccine, Recombinant

Human Papillomavirus Bivalent (Types 16, 18) Vaccine, Recombinant

Influenza A (H1N1) 2009 Monovalent Vaccine

Influenza A (H1N1) 2009 Monovalent Vaccine

Influenza A (H1N1) 2009 Monovalent Vaccine

Influenza A (H1N1) 2009 Monovalent Vaccine

Influenza A (H1N1) 2009 Monovalent Vaccine

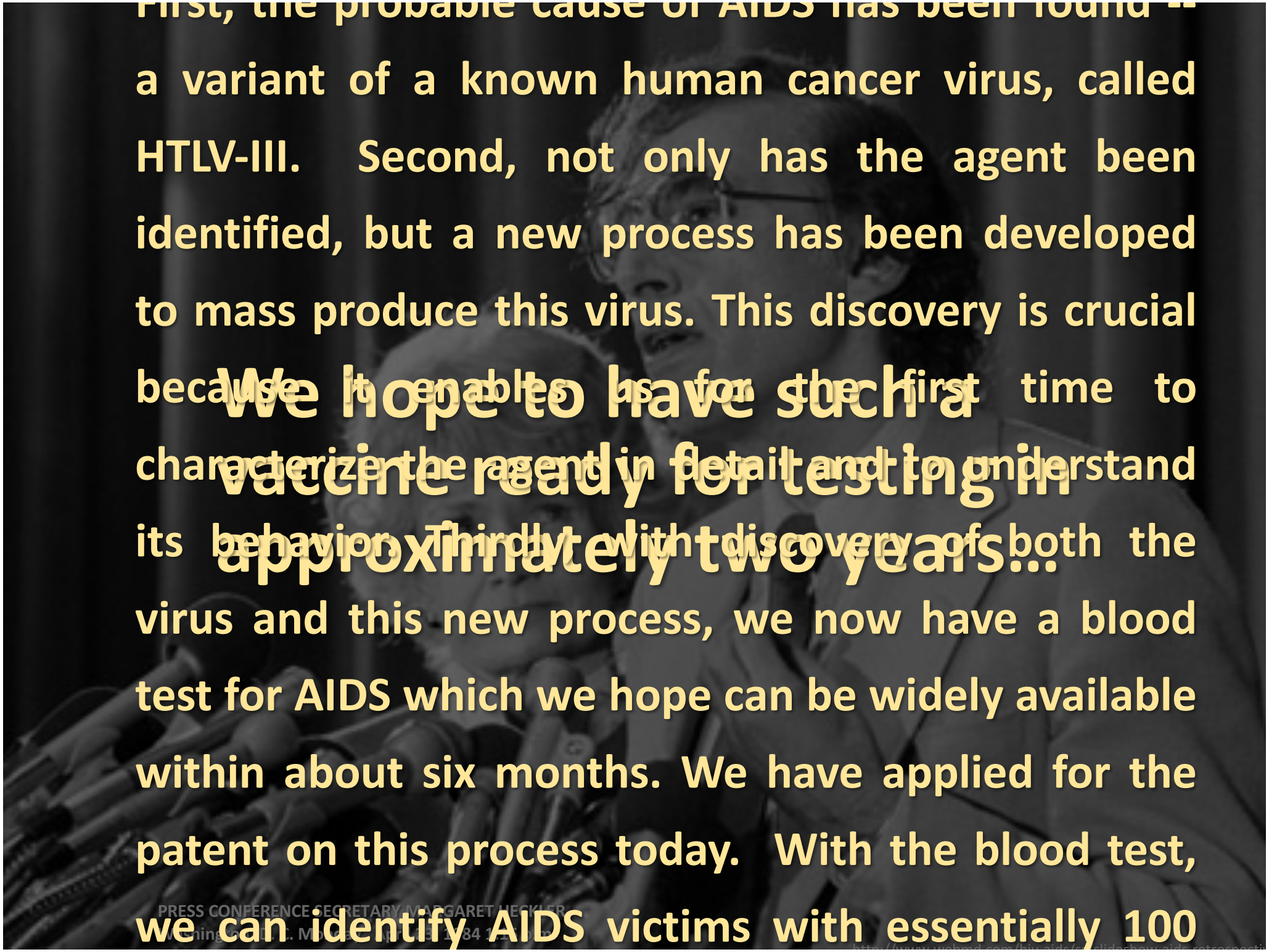
Influenza Virus Vaccine, H5N1 (for National Stockpile)

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

Influenza Vaccine, Adjuvanted

Successful Vaccines To Date

Largely a triumph of empiricism, luck and fortuitously tractable targets

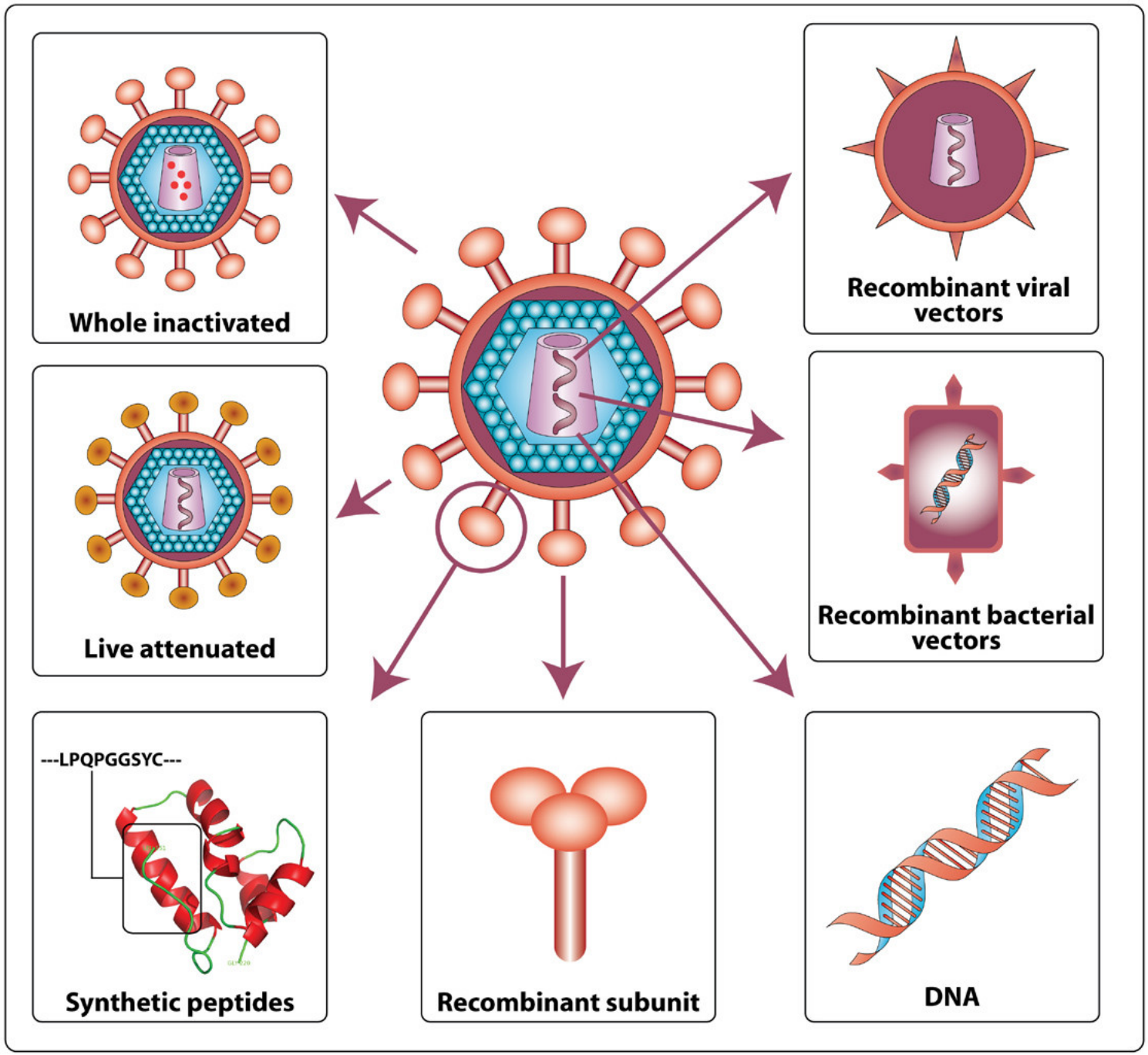

First, the probable cause of AIDS has been found -- a variant of a known human cancer virus, called HTLV-III. Second, not only has the agent been identified, but a new process has been developed to mass produce this virus. This discovery is crucial because it enables us for the first time to characterize the agent in detail and to understand its behavior. Thirdly, with discovery of both the virus and this new process, we now have a blood test for AIDS which we hope can be widely available within about six months. We have applied for the patent on this process today. With the blood test, we can identify AIDS victims with essentially 100
We hope to have such a vaccine ready for testing in approximately two years...
PRESS CONFERENCE SECRETARY MARGARET HECKLER

HIV Vaccine Efficacy Studies: 1984-2017

Vax 003	gp120 protein
Vax 004	gp120 protein
HVTN 502 (STEP)	Ad5
HVTN 503 (Phambili)	Ad5
RV144	Pox/protein
HVTN 702	Pox/Protein

Principles of Successful Vaccine Development

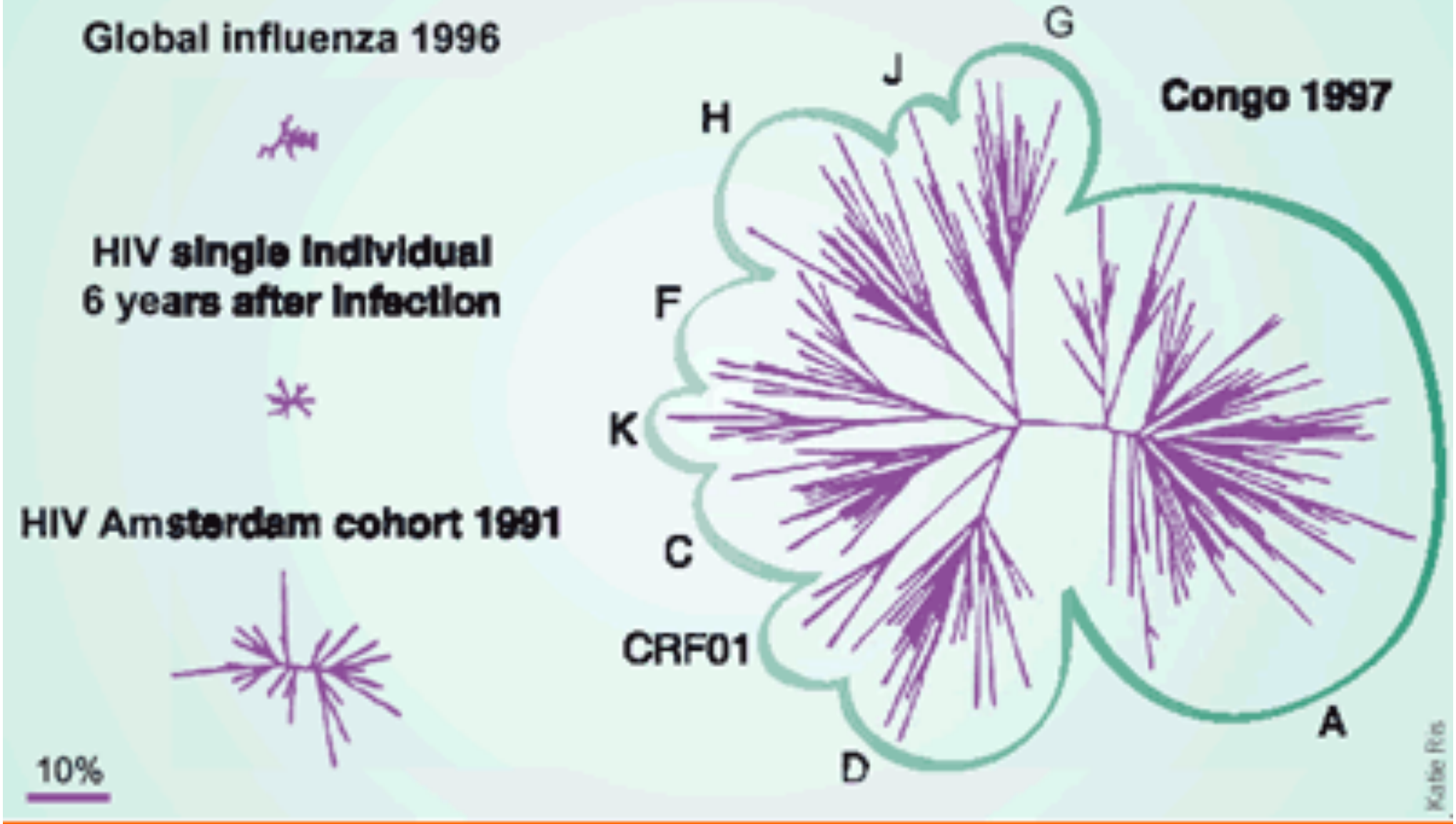
- Purpose of vaccines: Prevent infection vs. prevent disease
- Examples of naturally occurring (post-convalescent) immunity
- Immune correlate of protection
- Animal model



https://upload.wikimedia.org/wikipedia/commons/7/78/Various_approaches_for_HIV_vaccine_development.jpg

Challenges to HIV Vaccine Development

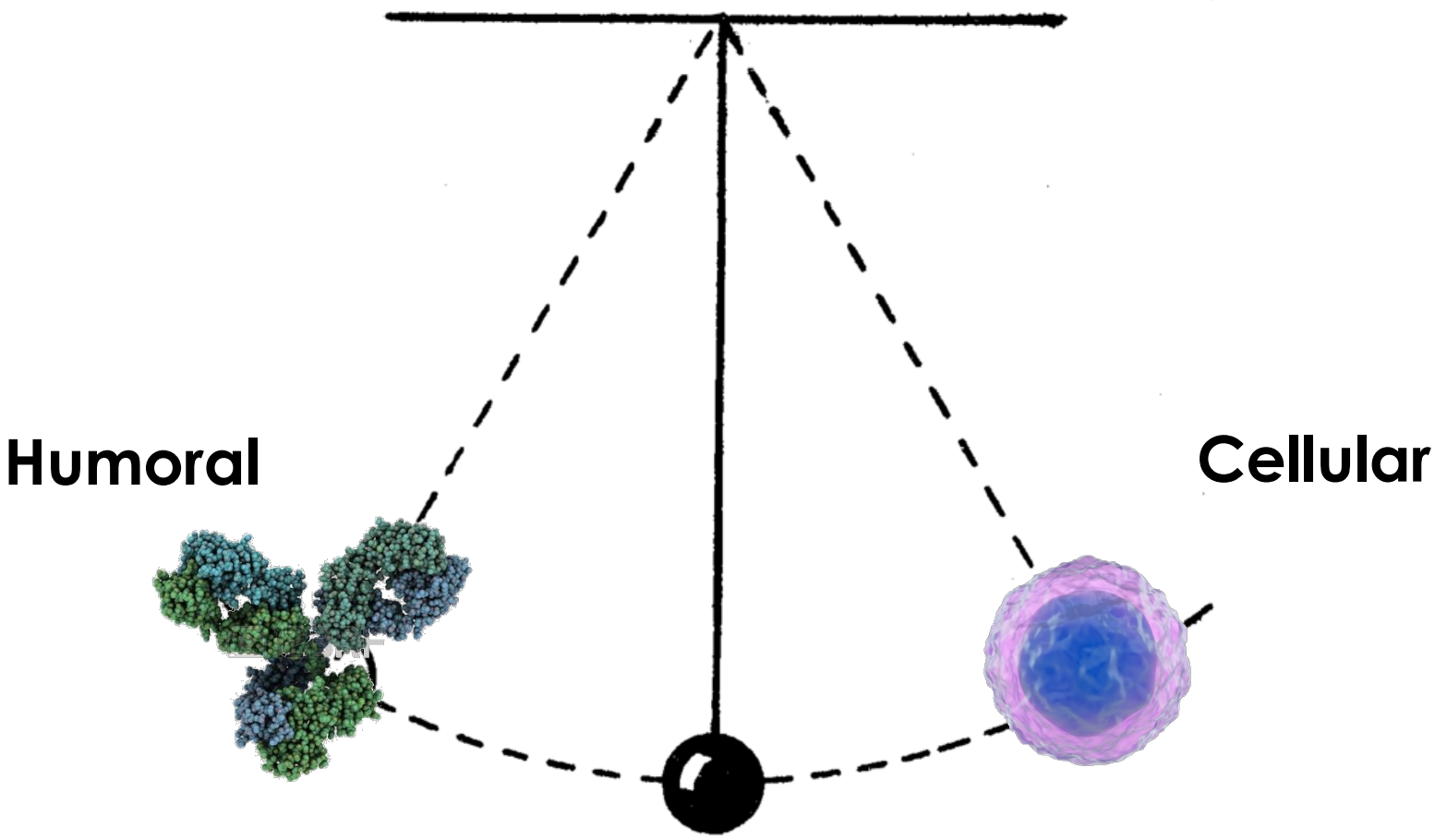
- No natural clearance; rare control
- Diversity, mutation, escape
- Attacks, eliminates/disables key immune cells
- Differential kinetics, virus, immunity
- Conformational complexity
- Glycoshield
- Integration/latency



Mechanisms of vaccine protection: no real correlate of protection from natural infection studies

- **Vaccine approaches: Targets**
  - **Humoral:**
    - **NAb (potency/breadth)**
    - **Non-NAb/Fc Functional Ab (ADCC, etc)**
  - **T cell immunity (Elite controllers)**
  - **Innate/Adjuvants**
- **Vaccine approaches: Immunogens**
  - **Prime boost**
  - **Killed, subunit, SOSIP trimer,**
  - **Live vectors**
    - **Replication incompetent**
    - **Replication competent**
  - **Nucleic acids: DNA, RNA**
  - **Consensus, Conserved, Mosaic inserts**
- **Immunization Scheme**

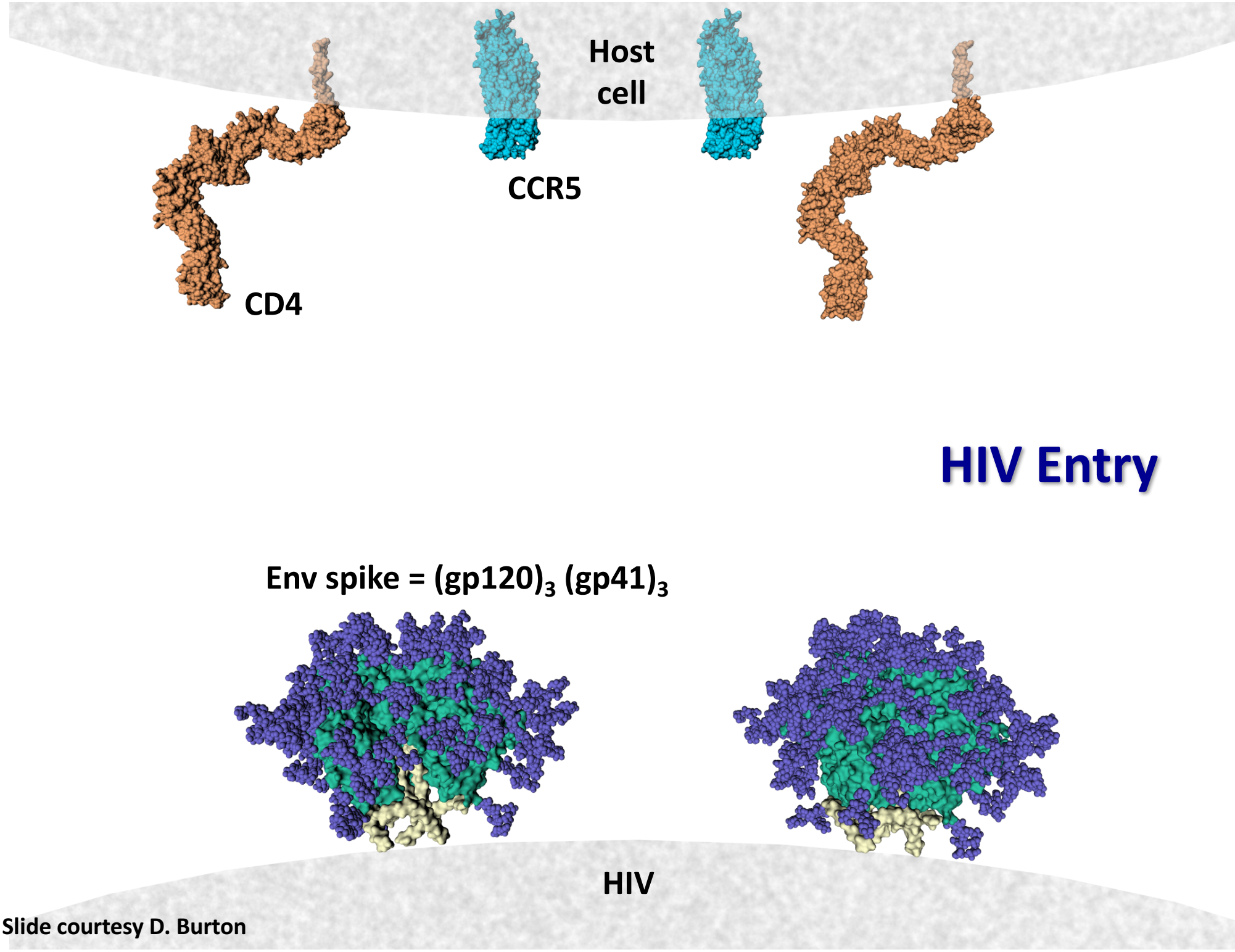
Humoral/Cellular Pendulum in HIV Vaccine Development



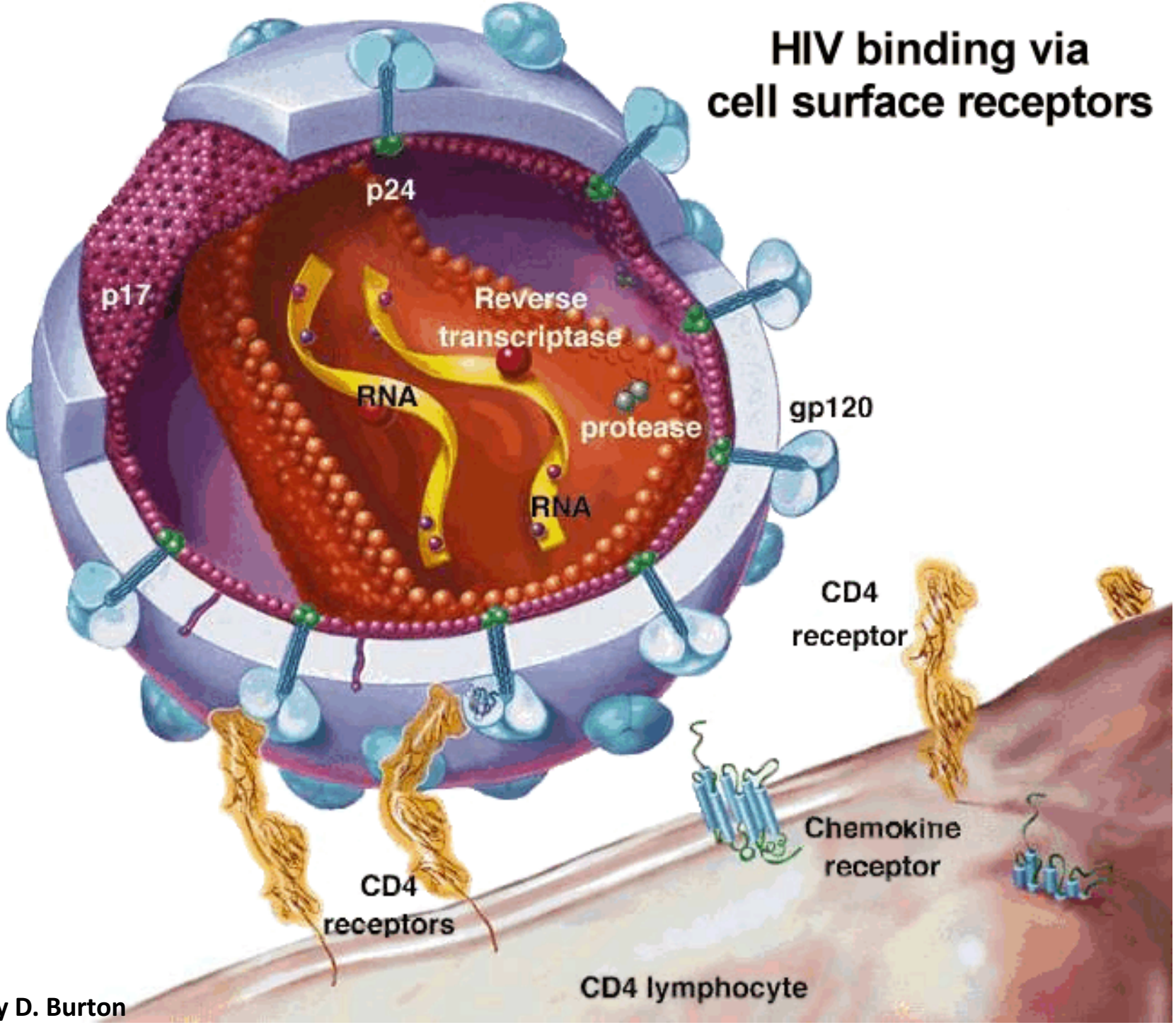
http://www.123rf.com/photo_13696208_chemical-structure-of-an-immunoglobulin-g-igg-antibody-molecule.html

https://bionews-tx.com/news/news-tags/t-cell/

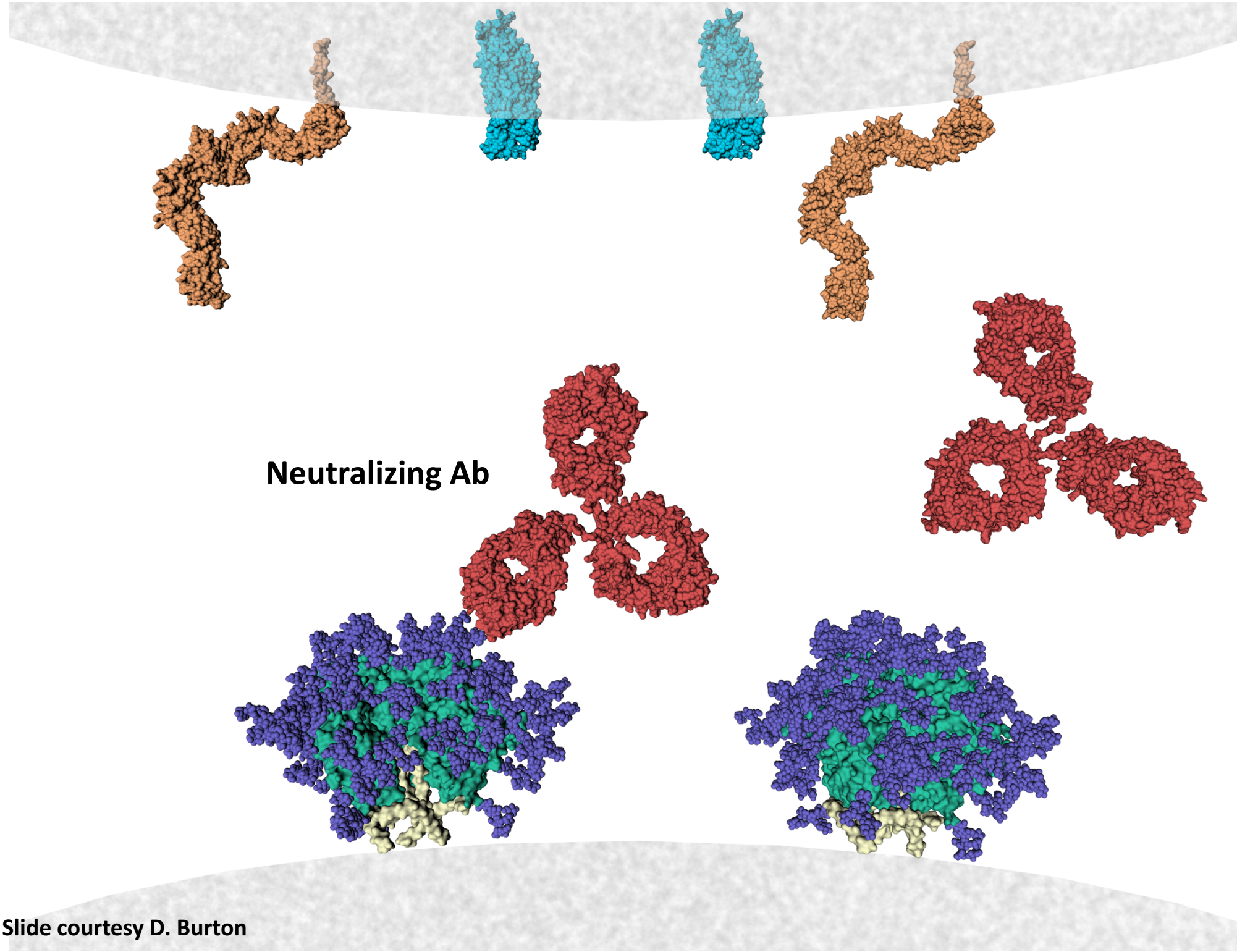
Neutralizing Ab directed vaccines



Slide courtesy D. Burton

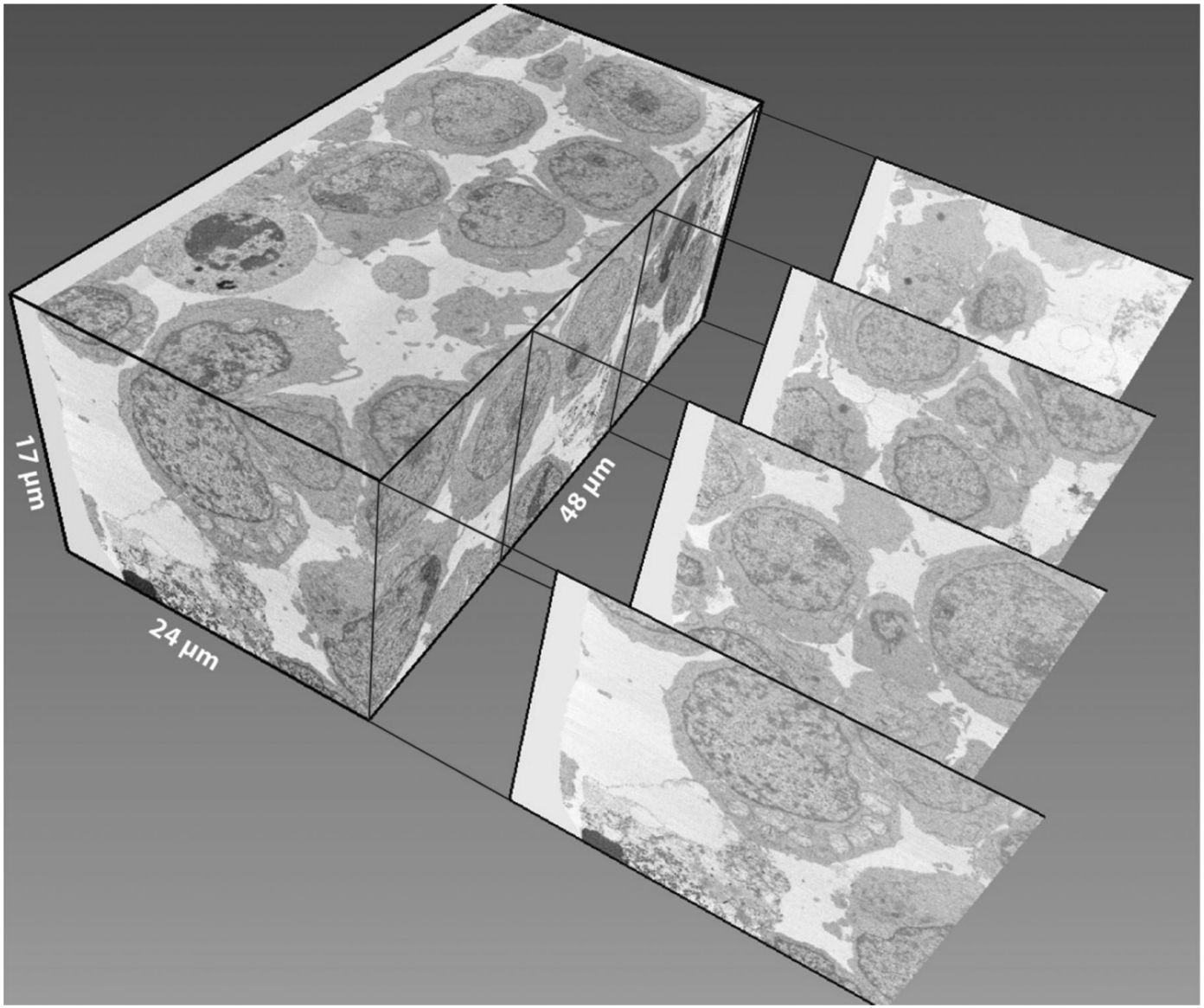


Slide courtesy D. Burton



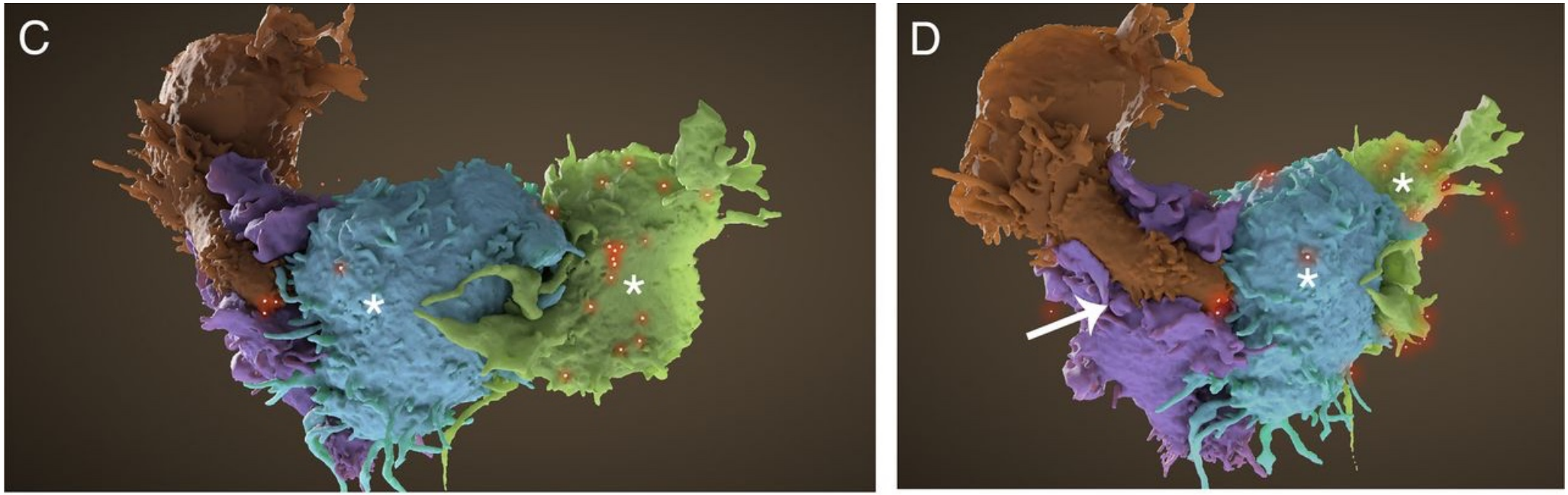
Slide courtesy D. Burton

FIB-SEM imaging reveals virological synapses between infected and uninfected T cells.



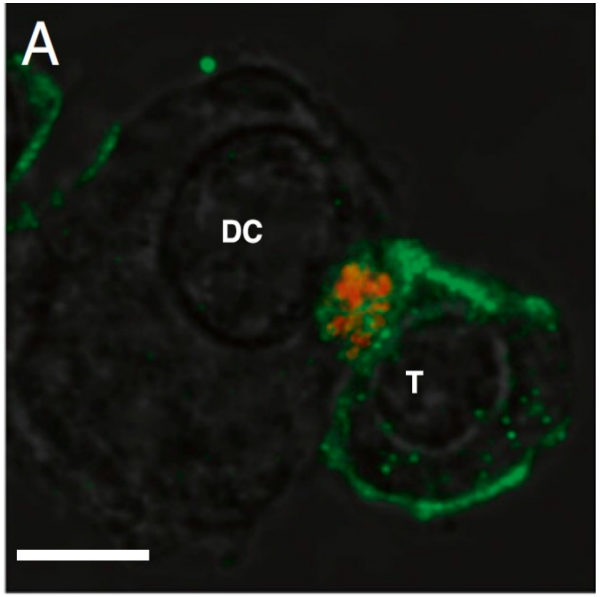
Thao Do et al. J. Virol. 2014;88:10327-10339

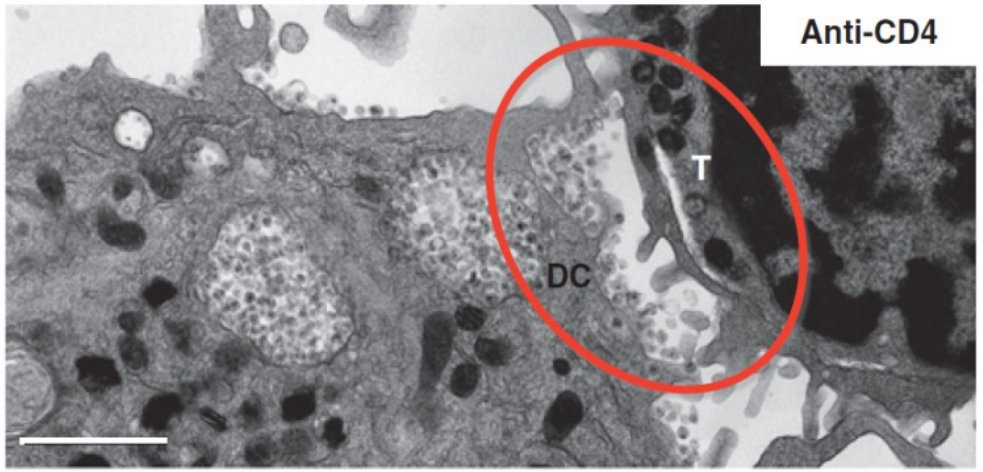
Virologic Synapses Pose a Challenge to Nab Blockade of Viral Transmission

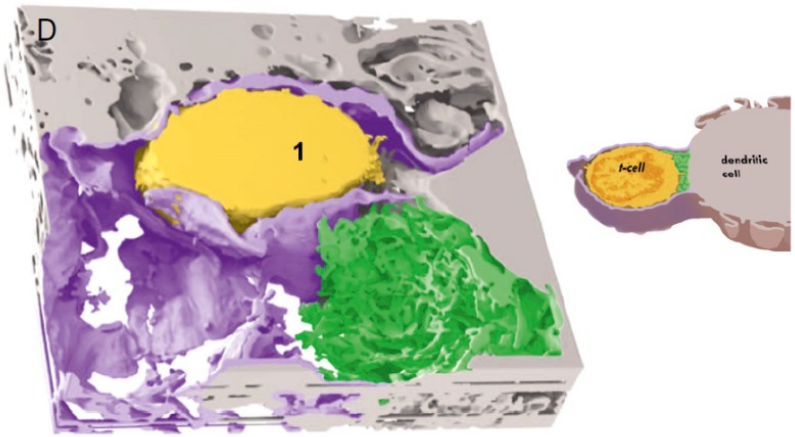


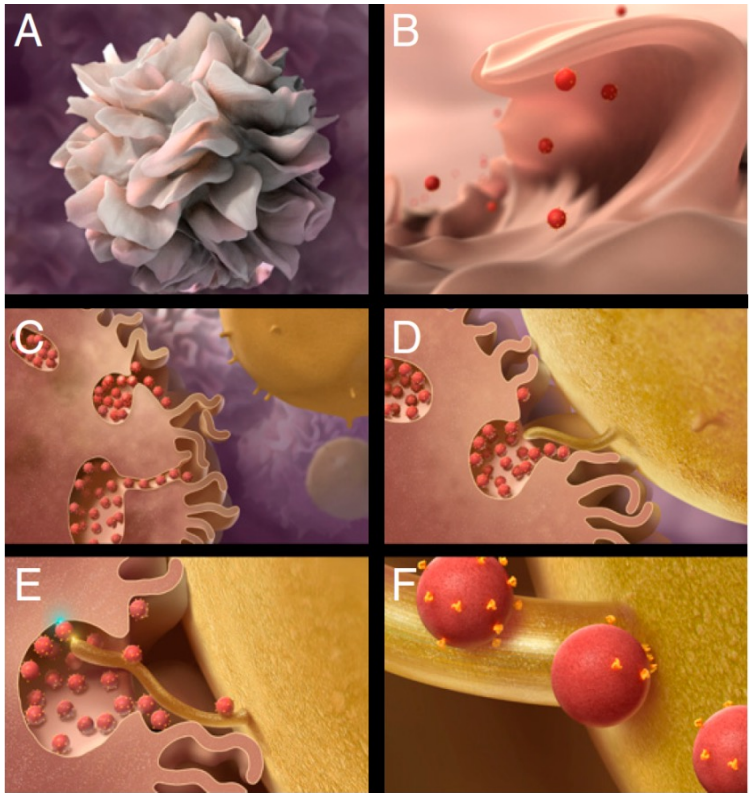
Thao Do et al. J. Virol. 2014;88:10327-10339

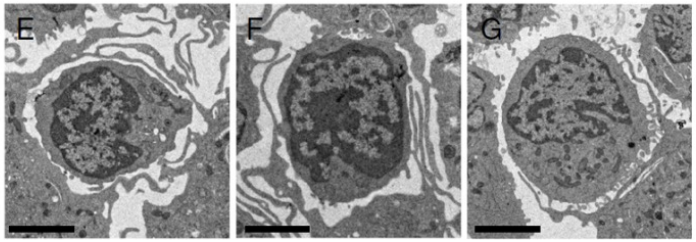
Virologic Synapses Pose a Challenge to Nab Blockade of Viral Transmission









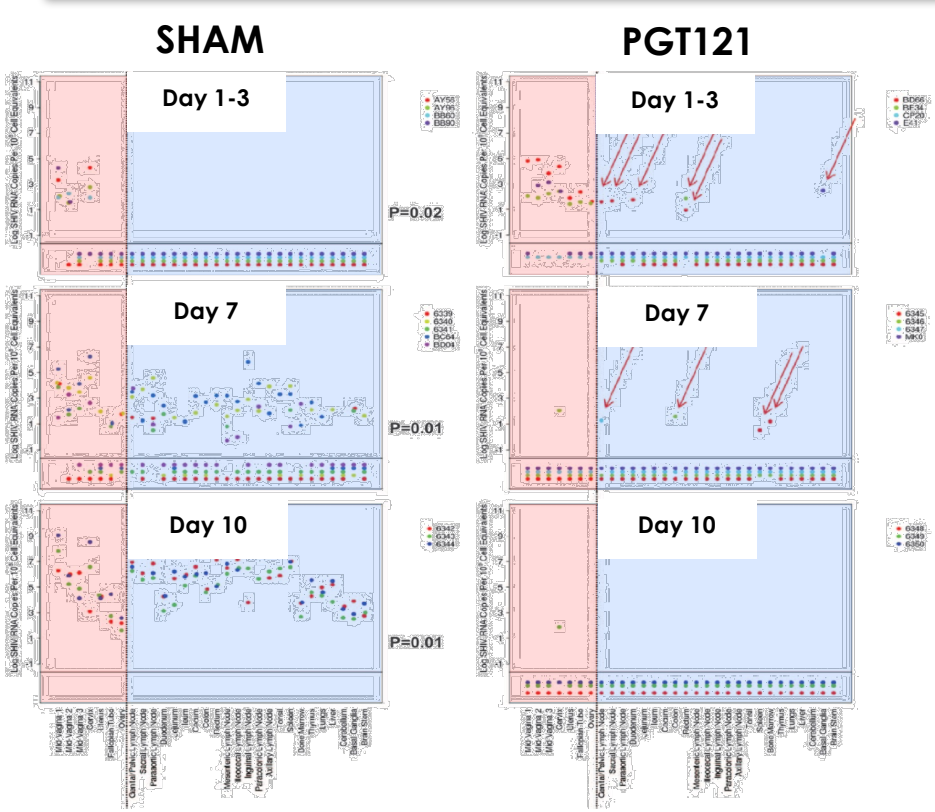


13336–13341 | PNAS | July 27, 2010 | vol. 107 | no. 30

HIV-1 ANTIBODIES Science 2 SEPTEMBER 2016 • VOL 353 ISSUE 6303

Antibody-mediated protection against SHIV challenge includes systemic clearance of distal virus

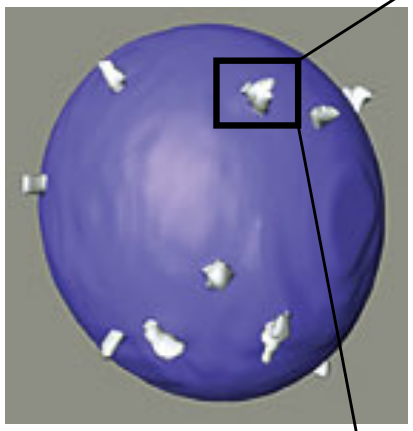
Jinyan Liu,[1] Khader Ghneim,[2] Devin Sok,[3] William J. Bosche,[4] Yuan Li,[4] Elizabeth Chipriano,[4] Brian Berkemeier,[4] Kelli Oswald,[4] Erica Borducchi,[1] Crystal Cabral,[1] Lauren Peter,[1] Amanda Brinkman,[1] Mayuri Shetty,[1] Jessica Jimenez,[1] Jade Mondesir,[1] Benjamin Lee,[1] Patricia Giglio,[1] Abishek Chandrashekar,[1] Peter Abbink,[1] Arnaud Colantonio,[5] Courtney Gittens,[6] Chantelle Baker,[6] Wendeline Wagner,[6] Mark G. Lewis,[6] Wenjun Li,[7] Rafick-Pierre Sekaly,[2*] Jeffrey D. Lifson,[4*] Dennis R. Burton,[3,8*] Dan H. Barouch[1,8*†]



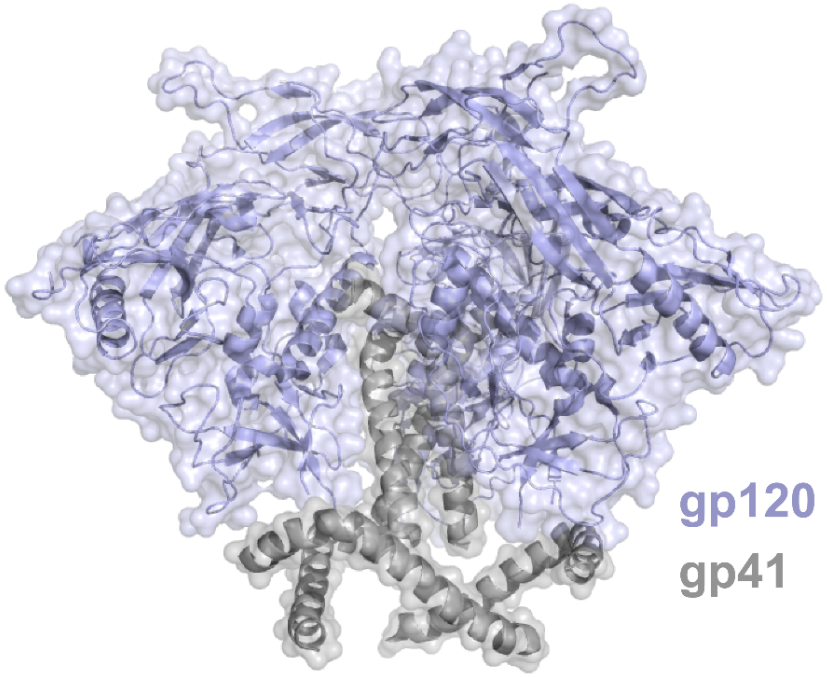
- **IVAG SHIV SF162P3 challenge**
- **Increased early distal vRNA+ tissues with bNAb PGT121 vs. sham control**
- **Adoptive transfer transmissible virus present early at distal sites with PGT121**
- **Virus cleared by day 10**

Cf: Hessell, et al, *Nat Med*. 2016

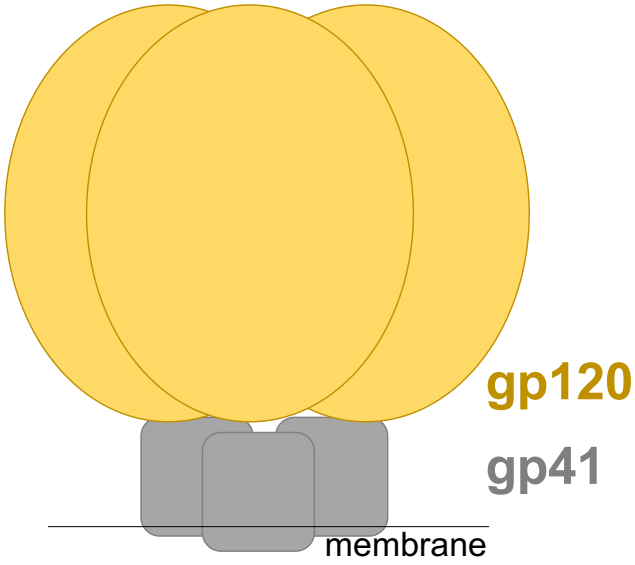
The HIV Env spike, sole target of nAbs, is a metastable trimer of heterodimers



HIV



Structural representation
(BG505 SOSIP.664)



Cartoon illustration

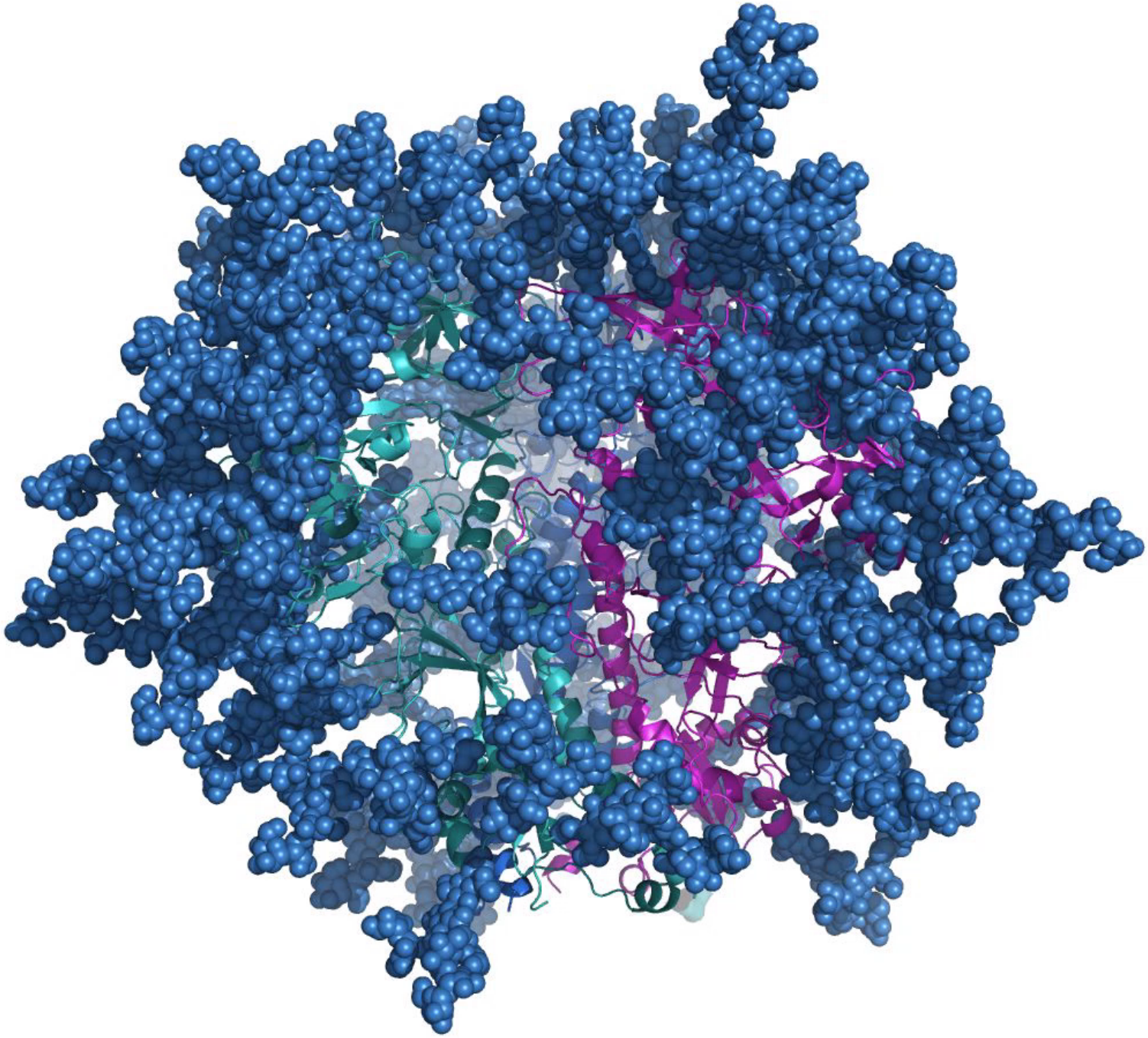
Zhu et al, Nature, 2006
Julien et al, Science, 2013
Lyumkis et al, Science, 2013
Pancera et al, Nature, 2014

Slide courtesy D. Burton

HIV Spike

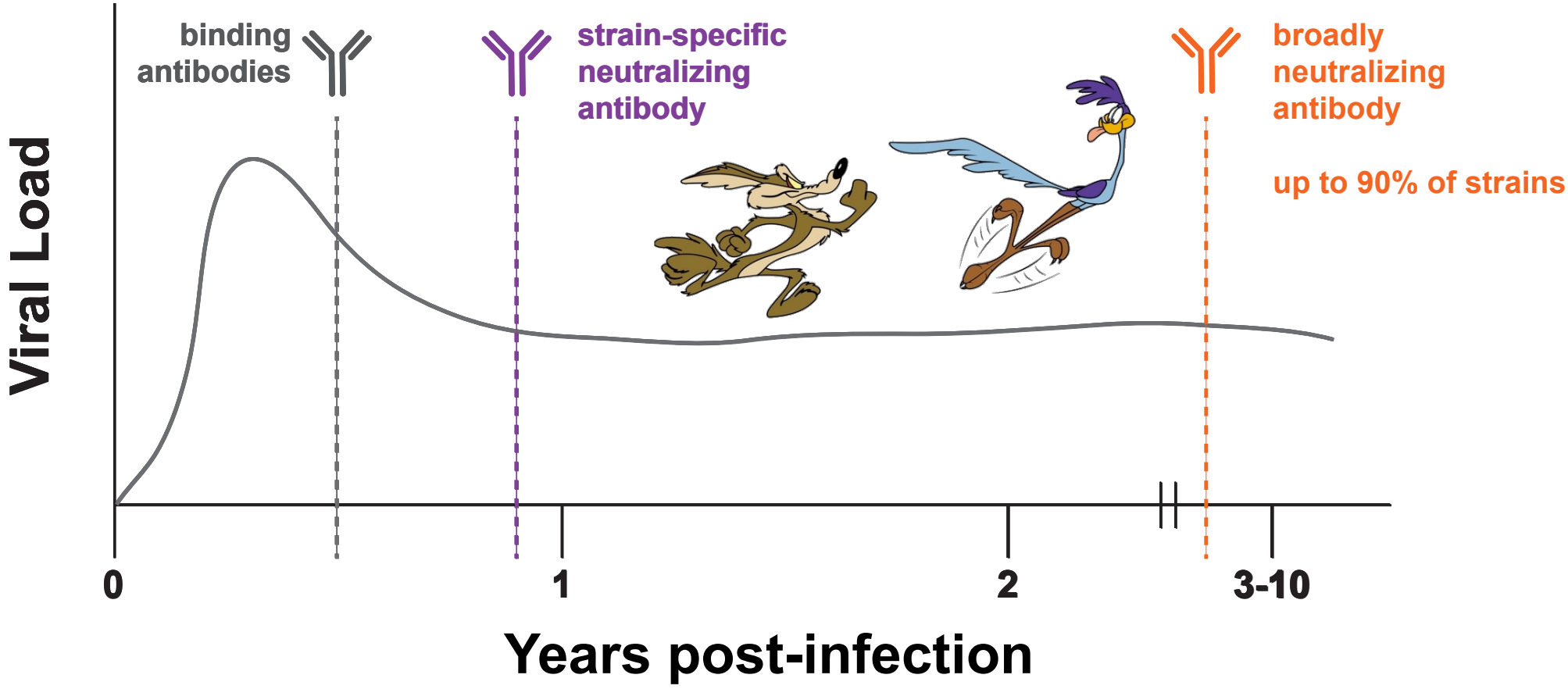
Jardine, Menis & Schief

Slide courtesy D. Burton



Slide courtesy D. Burton

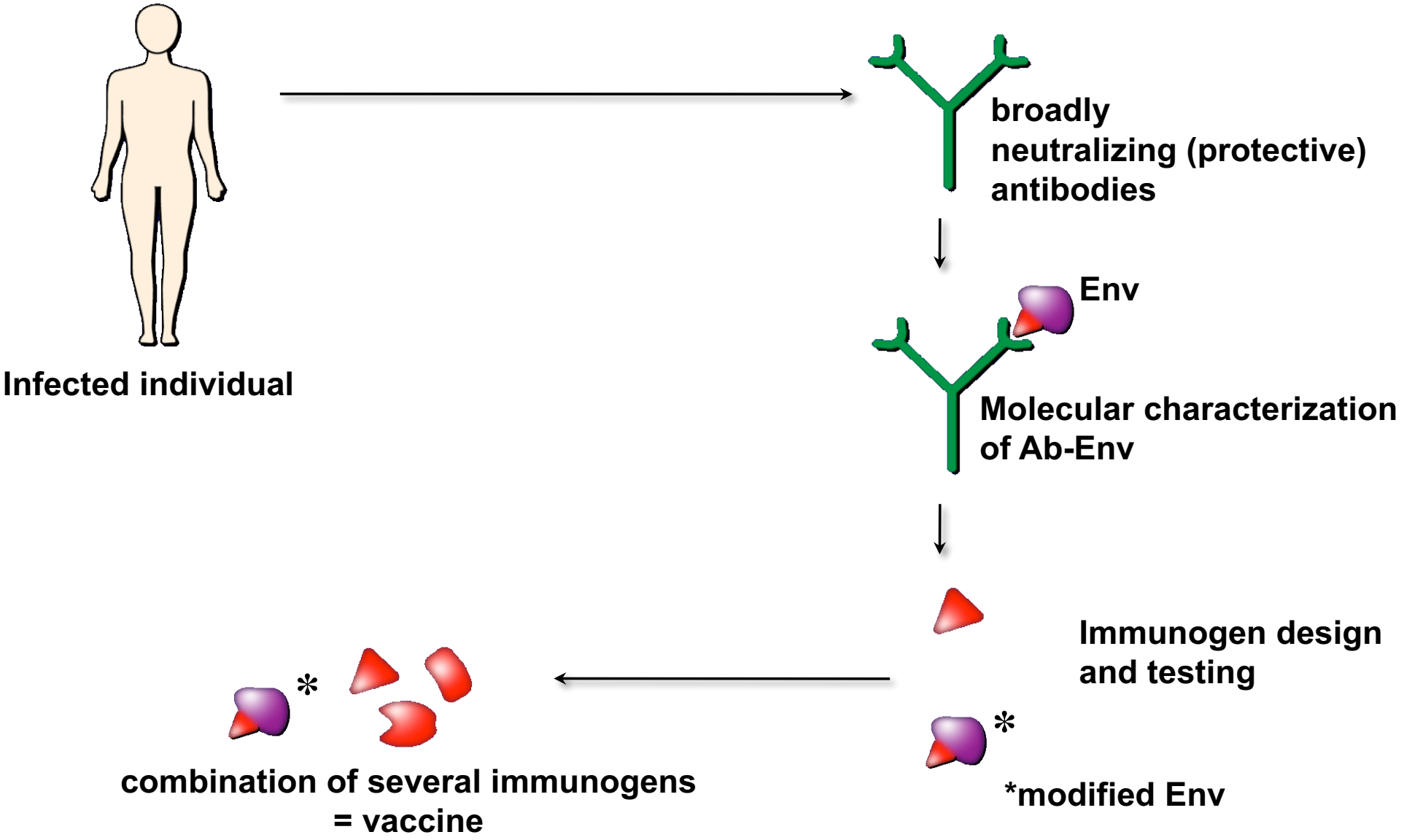
Despite the evasion tactics by HIV Env, up to 20% of chronically-infected individuals develop broadly neutralizing antibodies



Slide modified from D. Burton

Adapted from Mascola & Montefiori, Annu Rev Immunol, 2010

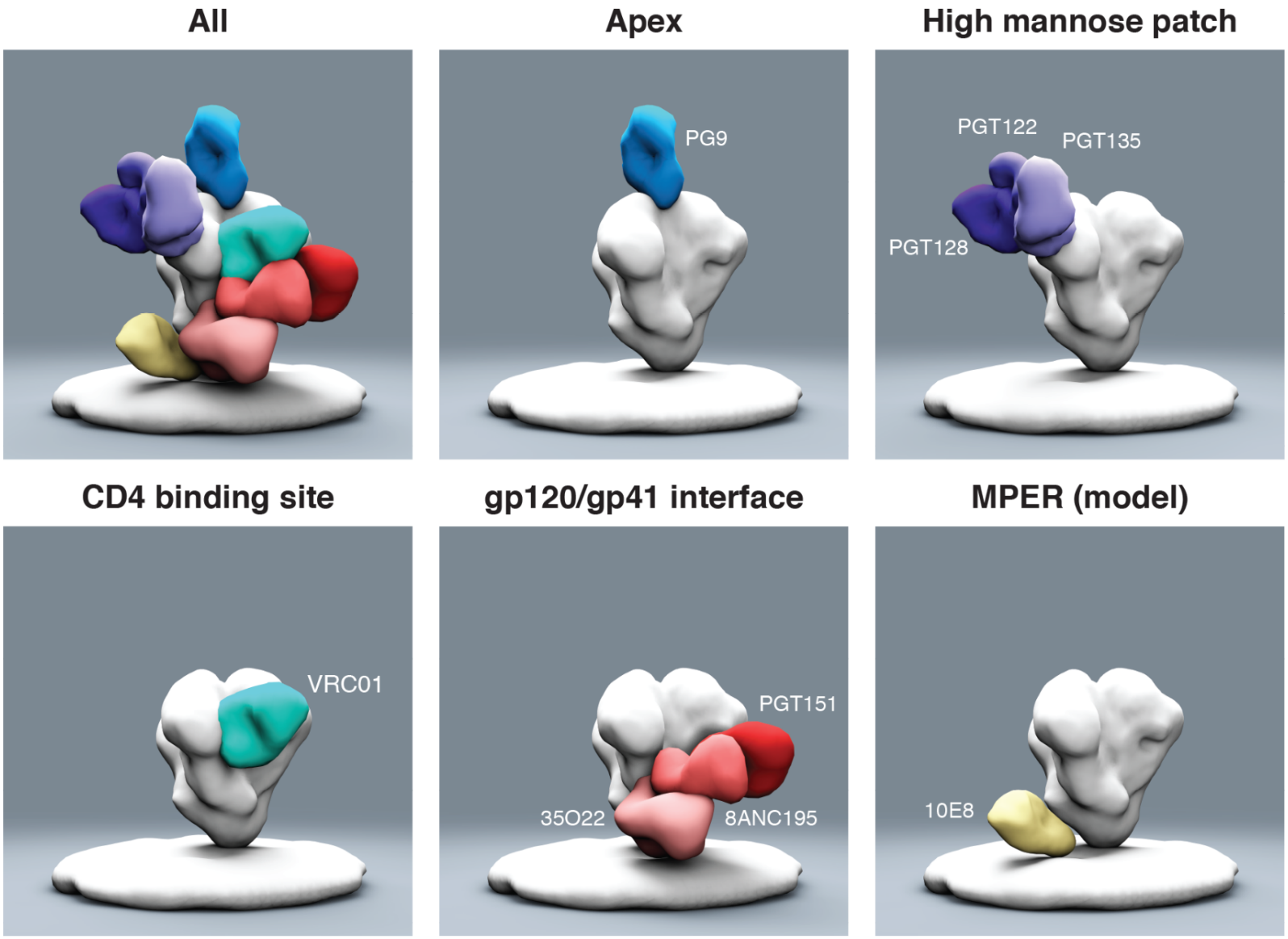
Reverse vaccinology 2.0



(adapted from Burton, Nat. Rev. Immunol., 2:706, 2002; Rappuoli et al, J Exp Med, 2016).

Slide courtesy D. Burton

Prototype bnAbs: binding regions

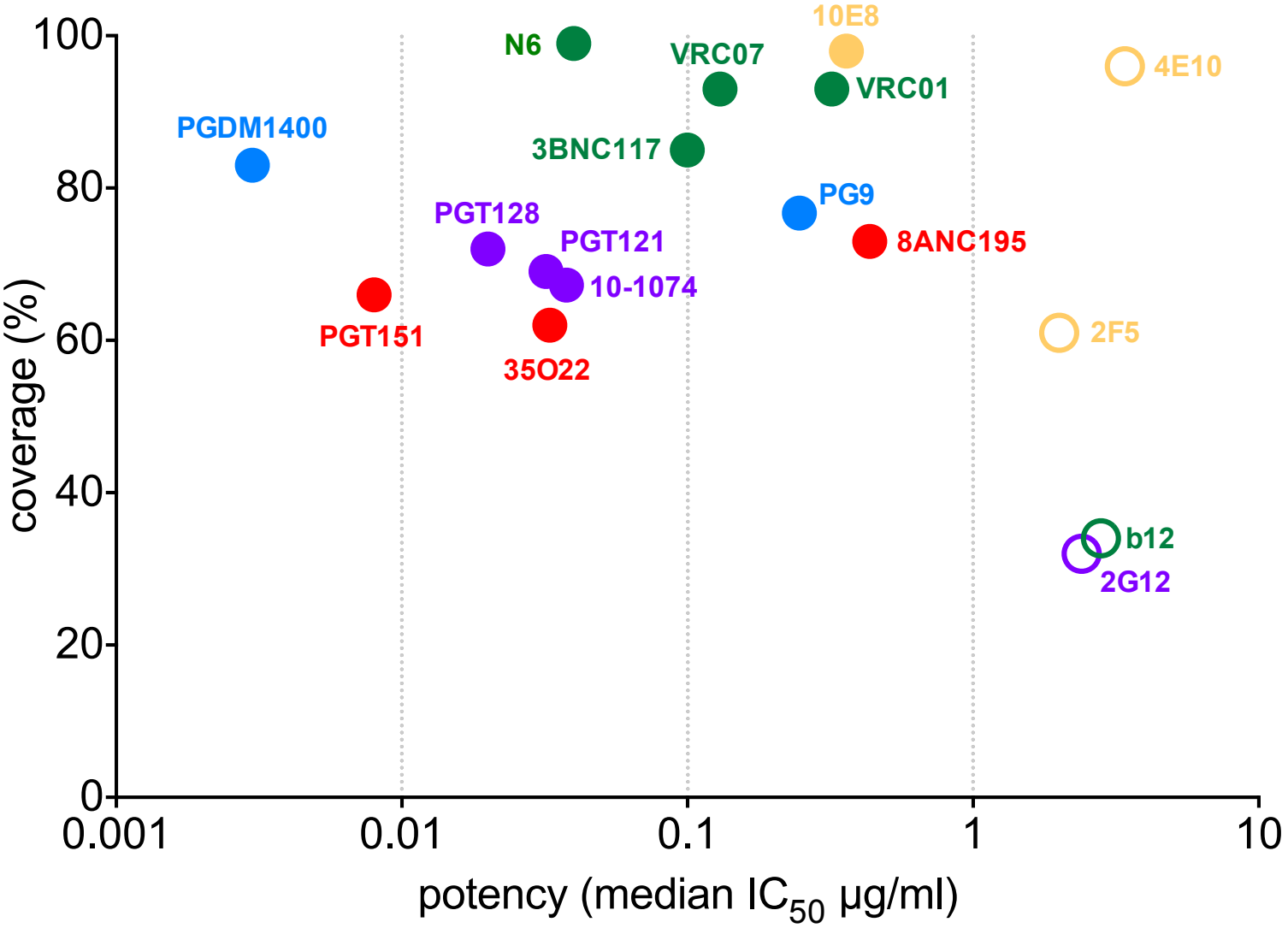


Burton & Hangartner, Ann Rev Imm, 2016

Ward et al

Slide courtesy D. Burton

Breadth and potency of prototype bnAbs from natural HIV infection



Slide courtesy D. Burton

Additional Obstacles to development of bnAb-targeted vaccines

- Oddball characteristics of bnMabs
  - CDR3 length
  - Somatic hypermutation
- Bridging the gap from antigen to immunogen
- Immunogens, Immunization scheme
  - Conformationally authentic trimers
  - Germline B cell receptor engagement
  - Sequential immunization
  - Persistence of antigen in vaccination vs. infection

Passive BNmAb Administration as Prophylaxis

- Obviates the "Antigen to Immunogen" challenge
- Efficacy demonstrated in NHP models
- Clinical studies in progress
- Multiple Abs may be necessary to for diversity coverage
- Administration/Costs: PK extending modifications
- Gene therapy approaches: AAV-vectors

Non-neutralizing Ab targeted vaccine

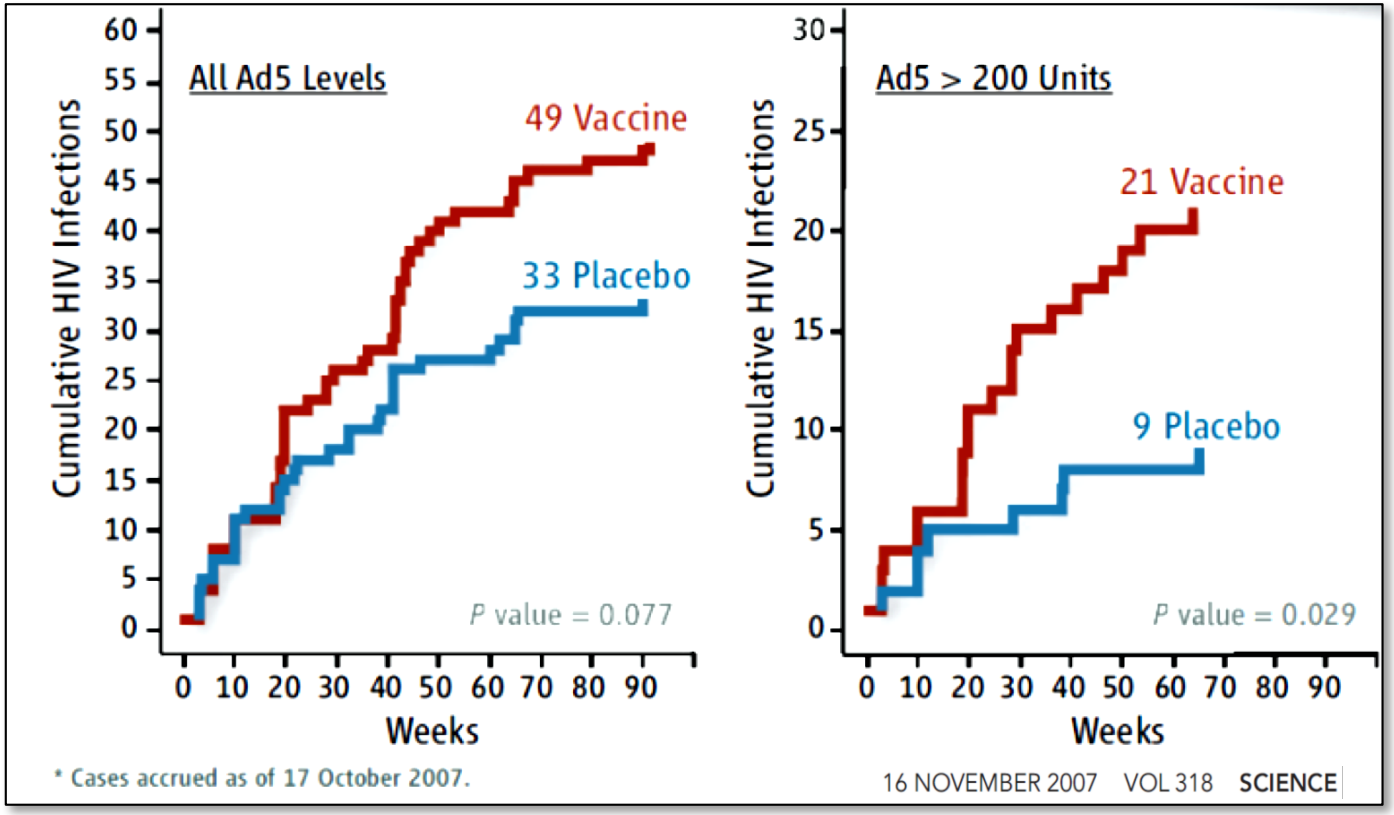
- Conceptual paradigm from RV144 "Thai Trial"
- Modest (31%) efficacy; minimal CD8+ T cell responses, nAb responses
- Immune correlates:
  - CD4+ T cell responses to Env
  - Non neutralizing, ADCC mediating responses to V1V2 region of Env, *in the absence of IgA responses*

Cellular Immunity Targeted Vaccines

Lancet 2008; 372: 1881–93

Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

*Susan P Buchbinder, Devan V Mehrotra, Ann Duerr, Daniel W Fitzgerald, Robin Mogg, David Li, Peter B Gilbert, Javier R Lama, Michael Marmor, Carlos del Rio, M Juliana McElrath, Danilo R Casimiro, Keith M Gottesdiener, Jeffrey A Chodakewitz, Lawrence Corey, Michael N Robertson, and the Step Study Protocol Team**

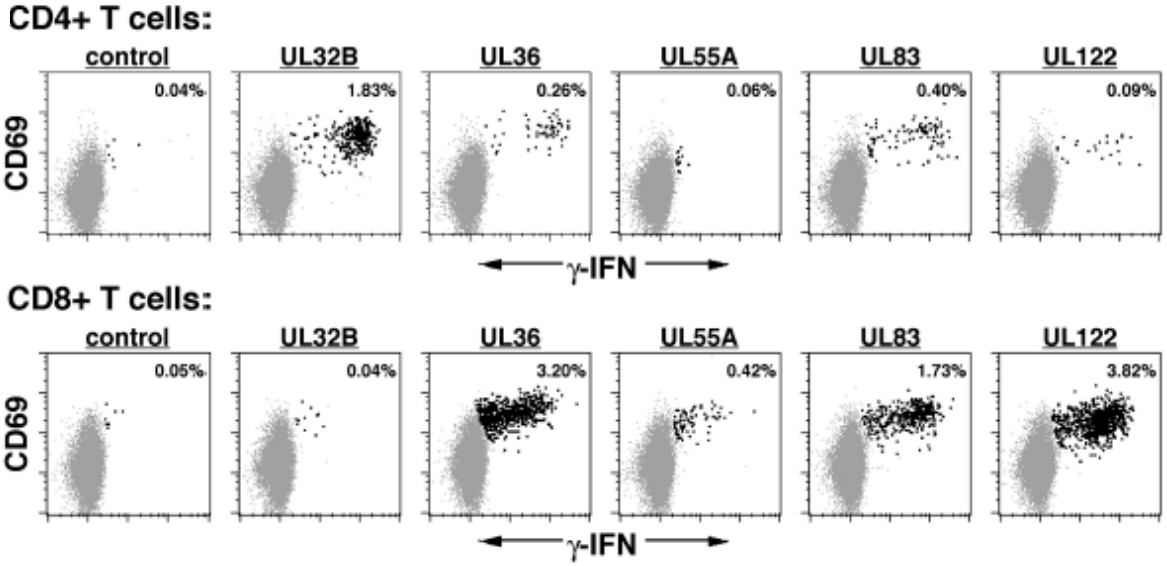


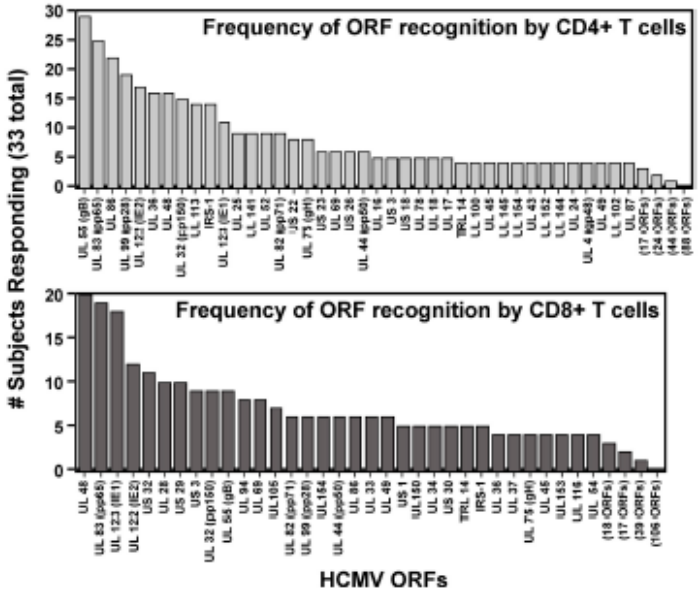
JEM Vol. 202, No. 5, September 5, 2005 673–685 ARTICLE

Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects

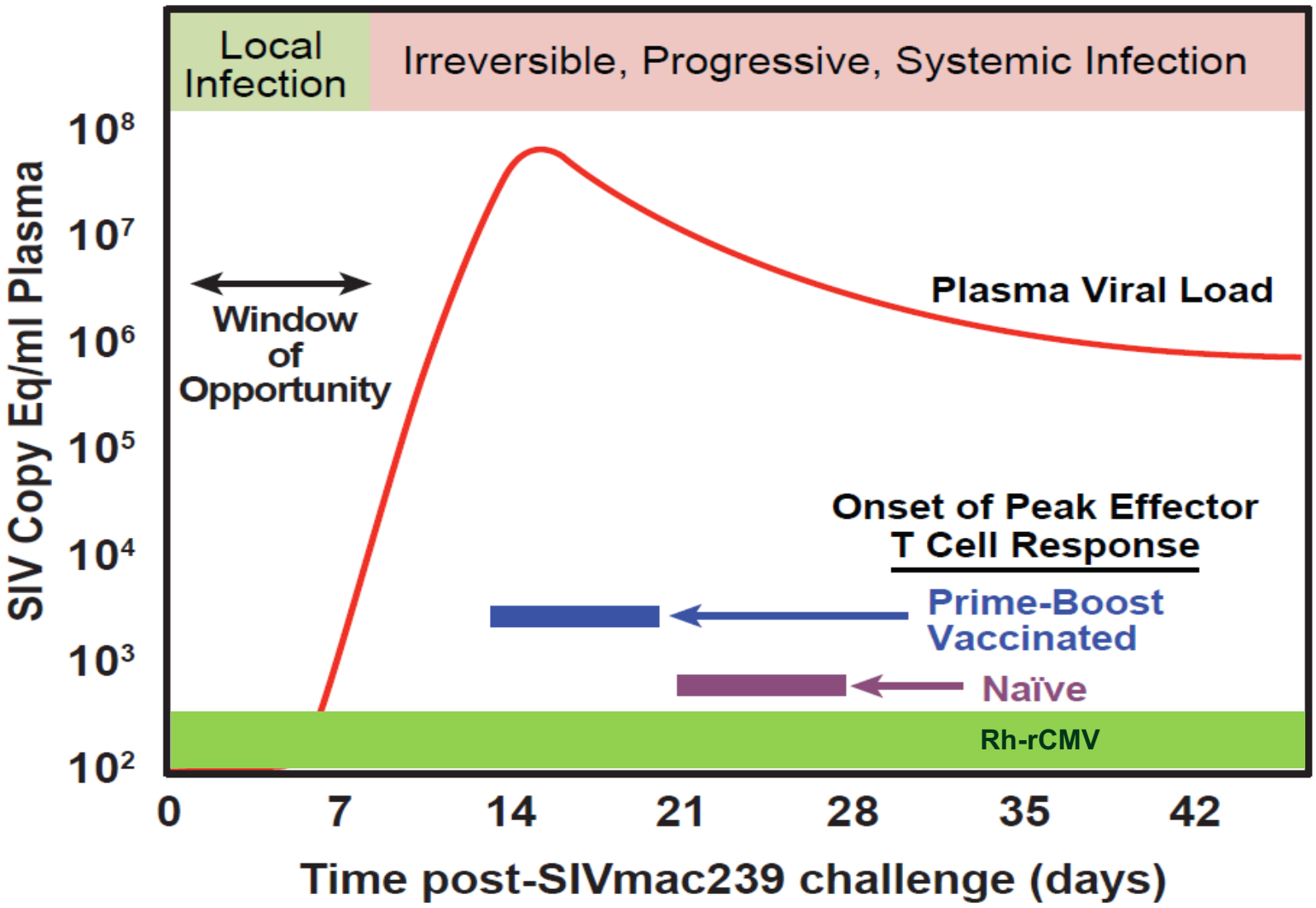
Andrew W. Sylwester,[1] Bridget L. Mitchell,[1] John B. Edgar,[1] Cara Taormina,[1] Christian Pelte,[1] Franziska Ruchti,[1] Paul R. Sleath,[2] Kenneth H. Grabstein,[2] Nancy A. Hosken,[2] Florian Kern,[3] Jay A. Nelson,[1] and Louis J. Picker[1]

[1]Vaccine and Gene Therapy Institute, Departments of Pathology and Molecular Microbiology and Immunology, and the Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR 97006
[2]Corixa Corporation, Seattle, WA 98104
[3]Institut für Medizinische Immunologie, Charité, 10098 Berlin, Germany





Kinetic Mismatch Barrier for AIDS Vaccines: "Too Little, Too Late"

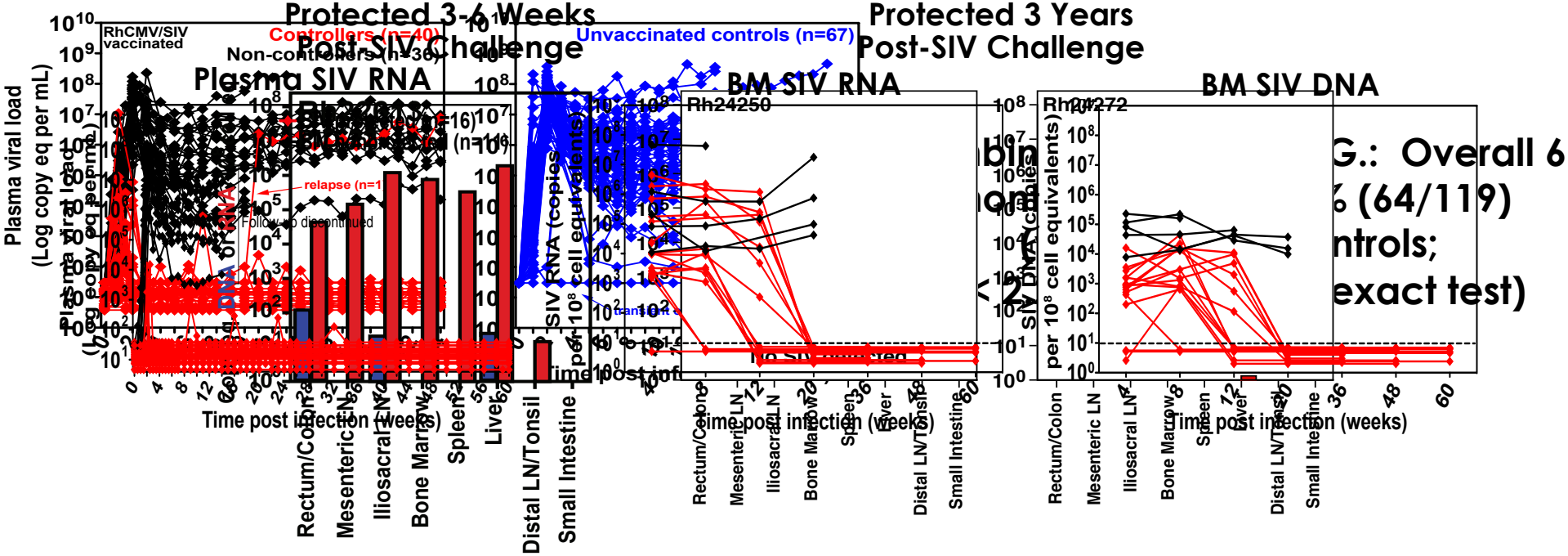


Picker, LJ, Hansen, SG, and Lifson, JD, Ann Rev Med, 2011

RhCMV as a Vaccine Vector: From Basic Research to an Unconventional Vaccine

- CMV cellular immune responses
  - Broadly specific CD4 and CD8 responses
  - Persistent virus→persistent responses
  - Effector memory differentiation skewed, immediate effector capacity
  - Broad tissue distribution
- Would a CMV-vectored SIV vaccine induce SIV-specific responses with these properties?
- If so, would these responses be associated with vaccine protection?

Cellular Only RhCMV-68.1/SIV Vaccine Responses (no Ab) Have Characteristics of CMV Induced Responses and Provide Post-Acquisition Stringent Control of Viral Replication



Hansen et al, Nat Med, 2009; Hansen et al, Nature, 2011; Hansen et al, Nature 2013, Hansen et al, in preparation.

Progressive clearance of residual virus from tissue over time!

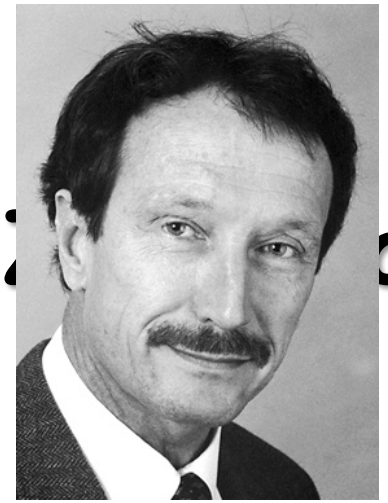
Science

RESEARCH ARTICLE

VOL 340 24 MAY 2013

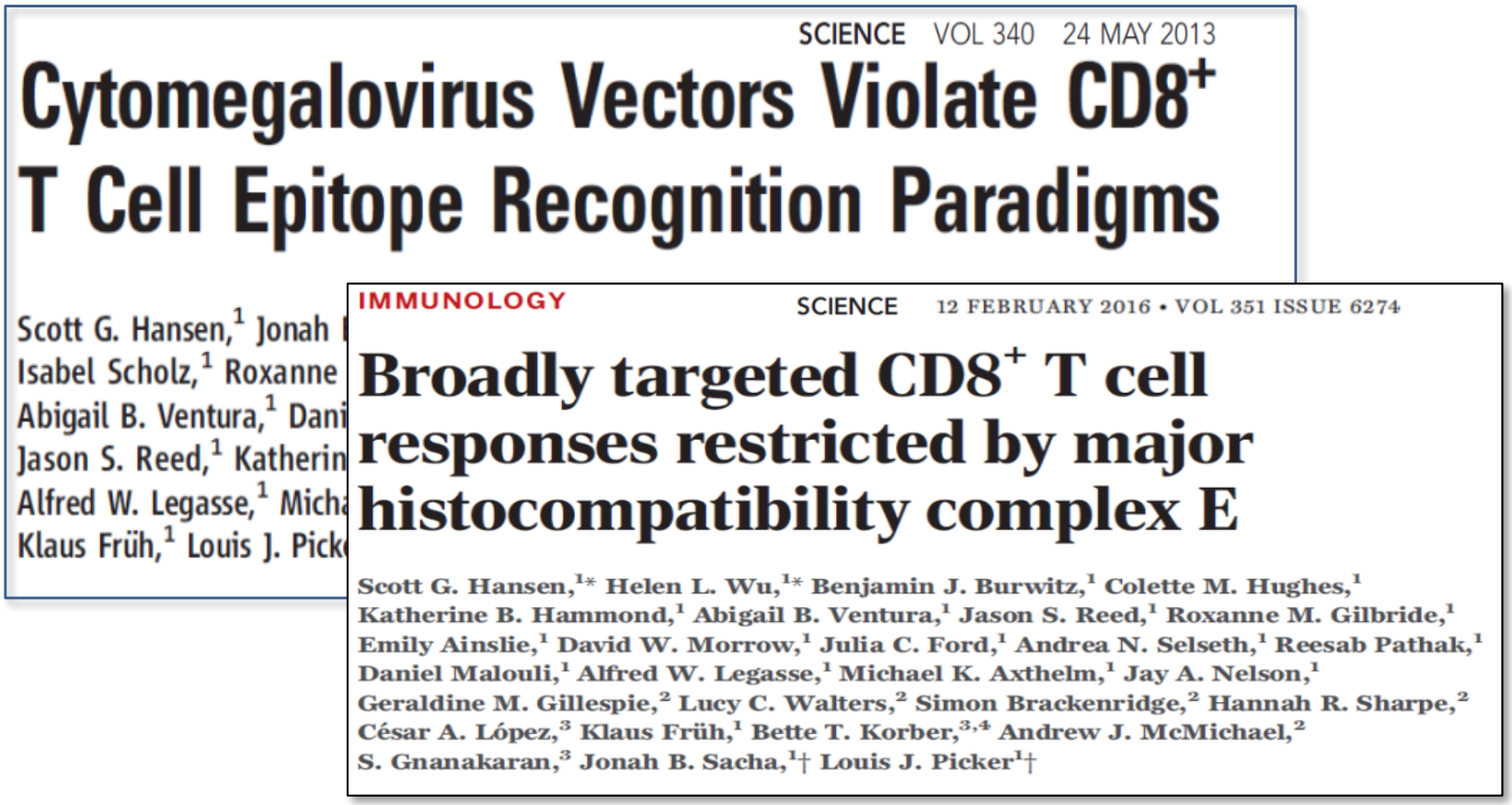
Cytomegalovirus Vectors Violate CD8+ T Cell Epitope Recognition Paradigms

Scott G. Hansen,[1] Jonah B. Sacha,[1] Colette M. Hughes,[1] Julia C. Ford,[1] Benjamin J. Burwitz,[1] Isabel Scholz,[1] Roxanne M. Gilbride,[1] Matthew S. Lewis,[1] Awbrey N. Gilliam,[1] Abigail B. Ventura,[1] Daniel Malouli,[1] Guangwu Xu,[1] Rebecca Richards,[1] Nathan Whizin,[1] Jason S. Reed,[1] Katherine B. Hammond,[1] Miranda Fischer,[1] John M. Turner,[1] Alfred W. Legasse,[1] Michael K. Axthelm,[1] Paul T. Edlefsen,[2] Jay A. Nelson,[1] Jeffrey D. Lifson,[3] Klaus Früh,[1] Louis J. Picker[1]*



http://www.nobelprize.org/nobel_prizes/medicine/laureates/1996/

CD8+ T Cell Responses Induced by Rh-CMV 68.1 Vectors Are Unconventionally Restricted (MHC Class II and IE)…



SCIENCE VOL 340 24 MAY 2013

Cytomegalovirus Vectors Violate CD8+ T Cell Epitope Recognition Paradigms

Scott G. Hansen,[1] Jonah
Isabel Scholz,[1] Roxanne
Abigail B. Ventura,[1] Dani
Jason S. Reed,[1] Katherin
Alfred W. Legasse,[1] Micha
Klaus Früh,[1] Louis J. Picke

IMMUNOLOGY

SCIENCE 12 FEBRUARY 2016 • VOL 351 ISSUE 6274

Broadly targeted CD8+ T cell responses restricted by major histocompatibility complex E

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…and Unconventional Responses Appear to be Responsible for Vaccine Protection!

Take Home Messages

- HIV vaccine development represents an extraordinary challenge, due to properties and biology of the target virus
- Considerable scientific progress has been made, but an efficacious vaccine remains elusive
- Ultimate success will likely depend on unconventional vaccine approaches
- The pressing need for a vaccine, and the potential impact of even a partially effective vaccine, motivate and justify continued research in this challenging area